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08/776,190	01/24/1997	HANS-PETER JOSEL	P564-7002	1643

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EXAMINER
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ART UNIT	PAPER NUMBER
1639	38

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/776,190	Josel et al
Examiner	**Art Unit**
Maurie G. Baker, Ph.D.	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *7/23/02 and 1/23/03*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *72-89 and 100-106* is/are pending in the application.

4a) Of the above, claim(s) *78, 79, 82, 89, and 102* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *72-77, 80, 81, 83-88, 100, 101, and 103-106* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☒ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Please note: The number of Art Unit 1627 has been changed to 1639. Please direct all correspondence for this case to **Art Unit 1639**.

1. The Responses filed July 23, 2002 (Paper No. 32) and January 23, 2003 (Paper No. 36) are acknowledged. No claims were added, amended or cancelled in these papers.

2. There is currently no allowable generic claim, thus claims 78, 79, 82, 89 and 102 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to non-elected species.

3. Applicant's attention is directed to MPEP § 803.02 (emphasis added) regarding election of species and Final Office Actions:

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. ***Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.***

4. Claims 72-77, 80, 81, 83-88, 100, 101 and 103-106 are examined in this action to the extent of the elected species.

Specification

5. The application now complies with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

Information Disclosure Statement

6. The Information Disclosure Statement (PTO-1449) filed August 26, 2002 is acknowledged; however, copies of the references cited therein are not in the file. The examiner is making efforts to locate these references; however, resubmission of these documents, if possible, by applicant would facilitate their consideration and would be greatly appreciated by the examiner. A signed copy of the PTO-1449 will be mailed as soon as the examiner obtains copies of the references.

Status of Rejections

7. All of the previous rejections are maintained. Applicant's arguments presented in Paper No. 32 are addressed after each rejection.

Maintained Rejections
Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 72-77, 80, 81, 83-88, 100, 101 and 103-106 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Applicant's claims are directed to conjugates that are defined in functional terms. The claims use generic terminology such as "hapten", "marker group", "solid phase binding group" "reactive side groups", "predetermined positions" and "non-immunologically reactive". These terms are set forth in the instant disclosure but the definitions are relative, broad and/or completely open-ended.

There are an unknown number of conjugates that would fall within the claimed genus for the following reasons. Claims 72, 74-77, 80, 83, 100, 101 and 103-106 contain no structural information whatsoever on the "haptens" and "marker groups" or "solid phase binding groups". The entities in question could encompass widely varying structures. Also, it is unclear how "non-immunologically reactive" a carrier would have to be in order to be encompassed by this limitation (see further rejections under 35 USC 112, second paragraph below). Instant claims 73, 81 and 84-88 set forth some structural information on either the hapten or marker group but still do not fully define the structure of the

claimed conjugates or specifically set forth a chemical structure for any of the entities that compose them.

The instant specification discloses *only* conjugates containing amino acid carriers with luminescent metal chelate marker groups and small organic molecule haptens that are attached through reactive amino side groups. Applicant's claimed scope represents only an invitation to experiment regarding other possible "haptens", "marker groups", "solid phase binding groups" and "reactive side groups". The claimed scope encompasses nucleotides as the "polymeric carrier" which are also not sufficiently described in the instant specification. Additionally, specifically with respect to claim 85, the recitation that the "polymeric carrier has a helical structure" is not supported by adequate description as there are no specific examples of such carriers and further how to attach the instant haptens and other groups thereto. Thus, the application fails to describe sufficient examples of conjugates that are within the scope of the presently claimed invention.

With respect to adequate disclosure of the scope of the presently claimed generic applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that

applicant had possession of the full scope of the claimed invention. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

Therefore it is deemed that the disclosure is neither representative of the claimed genus, nor does it represent a substantial portion of the claimed genus. Moreover, the claimed genus encompasses members which are yet to be prepared or envisioned. This further evidences that the structural features of the exemplified conjugates do not constitute support for the claimed genus or a substantial portion thereof.

Response to Arguments

10. Applicant's arguments filed July 23, 2002 (Paper No. 32) have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

11. Applicant argues that the claims are adequately described, citing portions of the specification and the prior art for support (Response, pages 4-8). The examiner's maintains that the definitions in the specification for the terms discussed in the rejection are *relative, broad* and *open-ended.* The instant claims give ***no specific structure*** for the entities that make up the claimed conjugates. Thus the claims could encompass an infinite number of variations. Note that "the essential goal of the description of the

invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978). Another objective is to put the public in possession of what the applicant claims as the invention so that the public may ascertain if the patent applicant claims anything that is in common use, or already known. *Evans v. Eaton*, 20 U.S. (7 Wheat.) 356 (1822).

12. The language of the specification should describe the claimed invention so that one skilled in the art can recognize what is claimed. A description of a compound in terms of its function fails to distinguish the compound from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175).

13. As stated in the rejection, the examiner pointed out that the specification discloses **very limited** examples of the preparation and use of the claimed conjugates. The entities that make up the claimed conjugates could encompass very different moieties of varying structures. Applicants arguments with respect to the broad teachings of the instant specification do not eliminate the above description problems.

14. Also, the rejection sets forth the need for representative examples in an unpredictable art that are necessary to demonstrate that applicant had possession of the full scope of the claimed invention. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure); all cited above. The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. See discussion of predictability in the art below (paragraphs 22& 23). Again, ***very limited examples*** have been provided in the instant case.

15. Moreover, several of the limitations of the instant claims are relative in nature. Applicant discusses this in stating that the "predetermined positions" "will be determined on a case-by-case basis" and that the "degree of non-reactivity required to meet this criterion ["non-immunologically reactive"] may vary on a case-by-case basis" (Response, page 6). It is the examiner's position that this further evidences that the instant specification is lacking in adequate description as it does not provide a clear standard for ascertaining the requisite locations and/or degree.

16. Lastly, an objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The examiner maintains because

of the breadth of the claims, the unpredictability of the art and the lack of any working examples, the above standard is not met. Thus the above rejection of claims 72-77, 80, 81, 83-88, 100, 101 and 103-106 under 35 U.S.C. 112, first paragraph is maintained.

17. Claims 72, 74-77, 80, 81, 83-88, 100, 101 and 106 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for conjugates where the polymeric carrier comprises amino acids as the monomeric units, does not reasonably provide enablement for conjugates where the polymeric carrier comprises nucleotides as the monomeric units. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is clear from applicant's specification how one might practice this invention with *specific* polymeric carriers that comprise amino acids (or modified versions thereof); however, there is insufficient guidance as to how to make/use conjugates where the polymeric carrier comprises nucleotides as the monomeric units. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;

(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are drawn to conjugates that comprise a polymeric carrier that is made up of monomer units that are amino acids (or modified versions thereof) or nucleotides. These conjugates further comprise 1-10 "hapten molecules" and 1-10 "marker groups or solid phase binding groups". These moieties are attached to the polymeric carrier via "reactive side groups" at "predetermined positions". Such represents very broad scope.

(3 and 5) The state of the prior art and the level of predictability in the art: Conjugates that comprise peptidic backbones that have certain specific "hapten molecules" and "marker groups or solid phase binding groups" attached thereto via "reactive side groups" are known in the art at the time of filing (see rejections below); however, only limited numbers of such conjugates were known and the specification gives no guidance to permit one of skill in the art to devise strategies for synthesis of conjugates with other types of backbones (i.e. sugar-phosphate backbone of DNA). The structures of possible variants are sufficiently diverse and one of ordinary skill would not be able to predict their structures.

The limitation that the "hapten molecules" and "marker groups or solid phase binding groups" are linked via "reactive side groups" (and specifically the "reactive amino side groups" or "reactive thiol side groups" recited in instant

claim 80 and elsewhere), adds to the unpredictability because it is unclear where such groups would be present in a conjugate comprising an oligonucelotide carrier. One of ordinary skill could not guess, *a priori*, how to make and use the claimed conjugates that comprise a polymeric carrier that is made up of monomer units that are nucleotides. Applicant's claimed scope of compounds represents only an invitation to experiment regarding possible "reactive side groups" that would link "hapten molecules" and "marker groups or solid phase binding groups" to a sugar-phosphate backbone. Moreover, although oligonucleotides are known to adopt helical structure (instant claim 85) the specification fails to teach how to make and use such helically structured carriers in the instant invention (i.e. where and to what groups are the "hapten molecules" and "marker groups or solid phase binding groups" attached?). Thus, the instant specification fails to identify that structure which is required for the claimed function.

(4) The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. Such persons of ordinary skill in this art, given its unpredictability, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have only provided examples of conjugates containing amino acid carriers with luminescent metal chelate marker groups and small organic molecule haptens that are attached through reactive amino side groups. Thus, the teachings of the instant specification coupled with the examples

only support conjugates comprising *specific* polymeric carriers that comprise amino acids (or modified versions thereof).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: In claims 72, 74-77, 80, 81, 83-88, 100, 101 and 106 there is only the broad recitation that the claimed conjugates comprise a polymeric carrier that is made up of monomer units that are amino acids (or modified versions thereof) or nucleotides. These conjugates further comprise 1-10 "hapten molecules" and 1-10 "marker groups or solid phase binding groups". These moieties are attached to the polymeric carrier via "reactive side groups" at "predetermined positions". However, the instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and using the full scope of the claimed conjugates, i.e. when the polymeric carrier comprises nucleotides. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Response to Arguments

18. Applicant's arguments filed July 23, 2002 (Paper No. 32) have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

19. Applicants argue that they have provided "direction and guidance of a more general nature to enable one of ordinary skill in the art to make and use alternative polymeric carriers" and also that they have provided "direction and guidance of a more general nature to enable one of ordinary skill in the art to make and use alternative reactive groups" (Response, page 7). It is noted that the above rejection is directed to the fact that the specification, while being enabling for conjugates where the polymeric carrier comprises amino acids as the monomeric units, does not reasonably provide enablement for conjugates where the polymeric carrier comprises nucleotides as the monomeric units.

20. As stated in the rejection, conjugates that comprise *peptidic backbones* that have certain specific "hapten molecules" and "marker groups or solid phase binding groups" attached thereto via "reactive side groups" are known in the art at the time of filing (see art rejections); however, only limited numbers of such conjugates were known and the specification gives no guidance to permit one of skill in the art to devise strategies for synthesis of conjugates with other types of backbones (i.e. sugar-phosphate backbone of DNA). The structures of possible variants are sufficiently diverse and one of ordinary skill would not be able to predict their structures. Importantly, the limitation that the

"hapten molecules" and "marker groups or solid phase binding groups" are linked via "reactive side groups" (and specifically the "reactive amino side groups" or "reactive thiol side groups" recited in instant claim 80 and elsewhere), adds to the unpredictability because it is unclear where such groups would be present in a conjugate comprising an oligonucelotide carrier.

21. The examiner's position is that one of ordinary skill could not guess, *a priori*, how to make and use the claimed conjugates that comprise a polymeric carrier that is made up of monomer units that are nucleotides. Applicant's claimed scope of compounds represents only an invitation to experiment regarding possible "reactive side groups" that would link "hapten molecules" and "marker groups or solid phase binding groups" to a sugar-phosphate backbone. Moreover, although oligonucleotides are known to adopt helical structure (instant claim 85) the specification fails to teach how to make and use such helically structured carriers in the instant invention (i.e. where and to what groups are the "hapten molecules" and "marker groups or solid phase binding groups" attached?). Thus, *the instant specification fails to identify that structure which is required for the claimed function.*

22. The general teachings referred to in applicant's arguments (Response, pages 7-8) are not deemed to be sufficient to enable the instant claims. As stated in the rejection, this is a very unpredictable area of the art. The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results

to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art.

23. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved. See *In re Fisher*, 57 CCPA 1099,427 F.2d 833,839,166 USPQ 18,24(1970). Additionally, the Board has held on the issue of unpredictability that "... the unpredictability of an art area alone may be enough to create a reasonable doubt as to the accuracy of statements in the specification." *Ex parte Singh*, 17 U.S.P.Q.2d 1714,1716 (B.P.A.I. 1990).

24. The instant claims are drawn to a product (conjugate). In order to be enabled for this product, the instant specification must enable how to make and use this product. As discussed above, the claimed invention is in a very unpredictable art. Most importantly, the instant specification fails to identify that structure which is required for the claimed activity. In the absence of such guidance, a practitioner of the art would have to resort to a substantial amount of experimental trial and error to produce any conjugates that have the required functional limitations. This trial and error would clearly constitute undue experimentation.

25. See MPEP 716.09: Once the examiner has established a prima facie case of lack of enablement, the burden falls on the applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would have been able to make and use the claimed invention using the disclosure as a guide. *In re Brandstadter*, 484 F.2d 1395, 179 USPQ 286 (CCPA 1973). The examiner maintains that one skilled in the art would ***not*** have been able to make and use the claimed invention using the disclosure as a guide for the reasons set forth in this action. Thus, the above rejection of claims 72, 74-77, 80, 81, 83-88, 100, 101 and 106 under 35 U.S.C. 112, first paragraph is maintained.

26. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

27. Claims 72, 77, 80, 85, 87, 100, 101, 103, 105 and 106 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 72, 77, 100, 101, 103, 105 and 106 recite "solid phase binding group". This is deemed to be indefinite as it is unclear what is the structure of such groups and the nature of the "solid phase binding" interaction. Is the phrase "solid phase binding" meant to encompass any type of binding – covalent, non-covalent, etc? Are the groups merely functionalities that can bind to any solid phase?

B. Claims 72, 80, 100, 101, 103, 105 and 106 recite "reactive side groups". It is unclear exactly where these groups are located, i.e. what is the "side" of the polymeric carrier? This is especially true when the carrier comprises nucleotide monomers.

C. Claims 72, 103, 105 and 106 recite "non-immunologically reactive". This is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a clear standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. That is, "non-immunologically reactive" under what conditions (in what assay)? A conjugate may be "immunologically reactive" in one assay and "non-immunologically reactive" in another. It is noted that the instant specification discusses the term "non-immunologically reactive" on page 16 (1st paragraph) but this discussion is completely open ended. For example, the specification states that a "non-immunologically reactive" amino acid sequence is one that "does not interfere with the test procedure in the intended application".

D. Claim 85 is indefinite because it recites that the "polymeric carrier has a helical structure". This is deemed to be indefinite because it is unclear how the carriers are to have such a structure. Specifically, is this structure is to be present before or after the addition of the "hapten molecules" and "marker groups or solid phase binding groups"?

E. Claim 87 is indefinite because it recites that the haptens are "pharmacologically active substances". The term "pharmacologically active" is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. That is, how "active" must a "substance" be in order to meet the limitations of this claim? What is the structure of such "substances"?

F. Claim 101 recites that the "reactive side groups coupling the hapten molecules and the reactive side groups coupling the marker groups or solid phase binding groups are alike". The term "alike" is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. That is, how "alike" must these side groups be in order to meet the limitations of this claim? Same reactivity? Same coupling reaction? Structurally "alike" before reaction? Completely chemically identical? This adds considerable confusion to the claim.

Response to Arguments

28. Applicant's arguments filed July 23, 2002 (Paper No. 32) have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

29. Applicants argue that each of the phrases rejected above "has been described in the specification and/or has a well-defined meaning within the art" (Response, page 8). The examiner respectfully disagrees. The phrases in sections C, E and F above are relative terms which renders the claims indefinite. Applicant points to various portions of the specification for support but this is not deemed to provide an adequate standard for ascertaining the requisite degree for this relative terminology.

30. Sections A, B and D are also not adequately explained to render the claims definite. Applicant is directed to MPEP 2173.05(a): [t]he meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed. Although applicant points to the specification and art and states that one of ordinary skill would understand these terms, the examiner disagrees. There is simply not enough information present to make the meaning of the terms readily apparent.

31. Also note the following from MPEP 2173.02: If the scope of the invention sought to be patented cannot be determined from the language of the claims with a reasonable degree of certainty, a rejection of the claims under 35 U.S.C. 112, second paragraph is appropriate. *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1973).

Maintained Rejections
Claim Rejections - 35 USC § 102

32. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

33. Claims 72, 74-77, 80, 81, 83, 86, 87, 101, 103, 105 and 106 remain rejected under 35 U.S.C. 102(b) as being anticipated by Bredehorst et al (Anal. Biochem., 1991; of record).

Bredehorst et al disclose a "novel trifunctional carrier molecule for the synthesis of hapten-fluorophore conjugates" (see Abstract). The carrier of Bredehorst et al consists of the 21 amino acids of the insulin A-chain; this reads on the limitations of claims 74 and 75 where the monomers are amino acids and the carrier has 21 monomeric units. One hapten (2,4-dinitrophenol (DNP)) and three fluorophores (fluorescein) are covalently attached to the carrier; see structure in Figure 1 of the reference. This reads on the limitations of claims 76 and 77 with respect to numbers of entities and claim 81 with respect to fluorescent "marker groups". The hapten is attached to a reactive amino group of the carrier (page 275, 1st column), which reads on the limitations of claim 80.

The carrier of Bredehorst et al also contains four Cys residues that are derivatized to S-sulfonates. As these modified residues are not naturally occurring amino acids, this reads on the "artificial" amino acids of claim 103. Also, the sulfonates are present in the charged form (to minimize hydrophobicity, see Bredehorst page 275, 1st column and Figure 1), which reads on the carrier containing charged groups (claim 83).

The hapten (DNP) has a molecular weight of about 170, which reads on the limitation of claim 86 and is a "pharmacologically active substance" (claim 87). As it is completely unclear how "alike" the reactive groups must be to be encompassed by the limitations of claim 101, the conjugate of Bredehorst is deemed to read on the conjugates of instant claim 101 as both the hapten and the fluorophore have a nitrogen in the attachment group (amine and azide, respectively).

With respect to the limitation that the amino acid carrier of the claimed conjugates is "non-immunologically reactive", Bredehorst et al disclose that their conjugate displays a decrease in non-specific binding (page 278, Table I) and higher sensitivity (page 277, 1st column) than entities without the carrier. Thus for the assay in question (binding to anti-DNP) the carrier clearly is "non-immunologically reactive". Note that the instant specification states on page 16 (1st paragraph) that a "non-immunologically reactive" amino acid sequence is one that "does not interfere with the test procedure in the intended application". The

carrier of Bredehorst et al clearly meets this limitation for their intended application.

Response to Arguments

34. Applicant's arguments filed July 23, 2002 (Paper No. 32) have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

35. Applicants set forth introductory statements to their arguments on page 10 of the Response. Applicants state that "the claimed invention relates to conjugates containing hapten molecules and marker groups or solid phase binding groups at specific predetermined positions in precisely defined stoichiometries"...going on to state that "[a]s a result of these predetermined positions, homogeneous compositions of conjugates are provided". In response to these arguments, it is noted that the features upon which applicant relies (i.e., specific predetermined positions in precisely defined stoichiometries and homogeneous compositions of conjugates) are not recited in the rejected claim(s). The instant claims do not contain reference to any ***specific*** predetermined position or any precisely defined stoichiometry. They also do not contain any reference whatsoever to homogeneous compositions. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Moreover, it is the examiner's position that some, if not all, of this terminology is relative (see paragraphs 26-31 above).

36. Applicants specifically argue the Bredehorst reference on pages 10-12 of the Response. They first argue that the reference does not teach or suggest "non-immunologically reactive" polymeric carriers. As stated in the rejection, the instant specification states on page 16 (1st paragraph) that a "non-immunologically reactive" amino acid sequence is one that "does not interfere with the test procedure in the intended application". The carrier of Bredehorst et al clearly meets this limitation for their intended application as Bredehorst et al disclose that their conjugate displays a decrease in non-specific binding (page 278, Table I) and higher sensitivity (page 277, 1st column) than entities without the carrier. Thus for the assay in question (binding to anti-DNP) the carrier clearly is "non-immunologically reactive" as defined in the instant specification.

37. Applicant also argues that the reference does not disclose artificial amino acids. As stated in the rejection, the carrier of Bredehorst also contains four Cys residues that are derivatized to S-sulfonates. As these modified residues are not naturally occurring amino acids, the examiner deems this to read on the "artificial" amino acids of claim 103. Applicants argue that "the artificial amino acids of the claimed invention relate to beta-amino-acids, gamma-amino-acids and the like". Claim 103 is *not limited* to such artificial amino acids.

38. Applicants argue that only a single hapten is conjugated in Bredehorst and thus the reference does not read on claim 101. Claim 101 clearly recites "the conjugate containing 1-10 hapten molecules". Applicants also argue that Bredehorst does not

disclose that the reactive groups are alike (instant claim 101). As stated in the rejection, it is completely unclear how "alike" the reactive groups must be to be encompassed by the limitations of claim 101. Thus it is the examiner's position that the conjugate of Bredehorst is deemed to read on the conjugates of instant claim 101 as both the hapten and the fluorophore have a nitrogen in the attachment group (amine and azide, respectively).

39. For these reasons, the rejection of claims 72, 74-77, 80, 81, 83, 86, 87, 101, 103, 105 and 106 under 35 U.S.C. 102(b) as being anticipated by Bredehorst et al is maintained.

40. Claims 72, 74, 75, 77, 80, 81, 83, 86, 87, 100, 101, 103, 105 and 106 remain rejected under 35 U.S.C. 102(b) as being anticipated by Buchardt et al (WO 92/20703; of record).

Buchardt et al disclose a peptide nucleic acid with a polyamide backbone which has various groups attached to the side chains of the backbone (see Abstract). The compounds of Buchardt et al read on the claimed conjugates as described below.

The "polymeric carrier" in Buchardt et al consists of the polyamide backbone of up to 61 units (see page 7 of the reference); this reads on the limitations of claims 74 and 75 where the monomers are modified amino acids and the carrier has up to 61 monomeric units. Buchardt et al specifically discloses

an example of a carrier with 12 units in Figure 5. As the peptide nucleic acids of Buchardt are not naturally occurring amino acids, this reads on the "artificial" amino acids of claim 103.

Applicant's recited definition of hapten (see instant specification page 8) encompasses any molecule that is a "pharmacological active substance". Nucleobases are known to be "pharmacologically active substances" (claim 87) and have molecular weights of greater than 100 (claim 86). The conjugate of Figure 5 has 10 nucleobases and also contains an acridine moiety. As acridine is a known fluorophore, this reads on the claimed "marker group". The compounds of Buchardt et al are made on a solid support via coupling at the amine end of the molecule and thus have a "solid phase binding group" of NH_2; see solid phase synthesis of Example 18(b) of the reference. Thus the conjugate of Buchardt in Figure 5 has 10 "haptens" (nucleobases), 1 fluorescent "marker group" (acridine) and one "solid phase binding group" (NH_2); this reads on the limitations of claim 77 and 100 with respect to numbers of entities and claim 81 with respect to fluorescent "marker groups". The hapten is attached to a reactive amino group of the carrier (amino group of backbone), which reads on the limitations of claim 80.

Buchardt et al also exemplifies a backbone containing a charged residue (see Figure 5), which reads on the carrier containing charged groups (claim 83). As it is completely unclear how "alike" the reactive groups must be to be encompassed by the limitations of claim 101, the conjugate of Buchardt is deemed to read on the conjugates of instant claim 101 as the hapten, the

fluorophore and the "solid phase binding group" have a nitrogen in the attachment group.

Lastly, as the conjugates of Buchardt clearly are disclosed to make helical structures (page 9, line 14 though page 10, line 32; pages 87-92 and Examples 56-61, for example), and that conjugates containing acridine (a fluorophore) are used in these experiments (page 91, line 6), claim 85 is anticipated.

Response to Arguments

41. Applicant's arguments filed July 23, 2002 (Paper No. 32) have been fully considered but are not found persuasive. The examiner's rationale is set forth below. *Please also see paragraph 35 above.*

42. Applicant argues that Buchardt does not teach or suggest a conjugate having hapten molecules and marker groups "coupled to reactive side groups at predetermined positions" (Response, page 12). As stated in the written description rejection above, the term "predetermined positions" is *not adequately described* in the instant specification. Moreover, as the sequence and structure of the conjugate of Buchardt is known (e.g. Figure 5 of the reference), this would read on groups "coupled to reactive side groups at predetermined positions".

43. Applicants argue that the reference "does not teach or suggest the methods for forming conjugates described in the present application". This is irrelevant as the instant

claims are drawn to products (conjugates), ***not*** methods. They go on to state that the "nucleic acid analogues described in *Buchardt et al.* will exhibit statistically controlled incorporation of hapten molecules and marker groups" and that they "may exhibit different stoichiometries"; as well as some of the conjugates of Buchardt will contain haptens and/or marker groups, while others will not (Response, pages 12-13). In response to these arguments, it is noted that the features upon which applicant relies (i.e. controlled incorporation, defined stoichiometries and precise compositions of conjugates) are not recited in the rejected claim(s). Additionally, as the sequence and structure of the conjugate of Buchardt is ***known*** (e.g. Figure 5 of the reference), these arguments are moot for this reason as well.

44. For these reasons, the rejection of claims 72, 74, 75, 77, 80, 81, 83, 86, 87, 100, 101, 103, 105 and 106 under 35 U.S.C. 102(b) as being anticipated by Buchardt et al is maintained.

45. Claims 72, 74, 75, 80, 86, 87, 88, 100 and 106 remain rejected under 35 U.S.C. 102(b) as being anticipated by Tam (US 5,229,490).

Tam discloses a "multiple antigen peptide" system where "a large number of antigens are bound to the functional groups of a dendritic core molecule" (see Abstract). These "multiple antigen peptide" systems read on the claimed conjugates as described below.

The "polymeric carrier" in Tam consists of a dendritic core molecule, which in Figure 1 is shown as consisting of 8 amino acid residues; this reads on the limitations of claims 74 and 75 where the monomers are amino acids and the carrier has 8 monomeric units. Eight peptide antigens (i.e. hapten) moieties are attached to the dendritic core molecule of Tam. The haptens are attached to reactive amino groups (Lys) of the carrier (see column 5, line 33-53), which reads on the limitations of claim 80.

Applicant's recited definition of hapten (see instant specification page 8) encompasses any molecule that is a "pharmacological active substance". The peptide antigens of Tam are known to be "pharmacologically active substances" (claim 87) and have molecular weights of greater than 100 (claim 86). The peptide antigens of Tam specifically read on the exact same "immunogenically reactive peptide epitope" haptens claimed in the instant claim 88. See discussion of peptide antigens found in Tam column 5, line 64 through column 7, line 64, especially the antigens set forth in Table 1).

The conjugates of Tam are made on a solid support via coupling at one end of the molecule (at the –OH moiety of the 1st amino acid of the carrier) and thus have a "solid phase binding group" of -OH; see solid phase synthesis described in Example 2 of the reference. Thus the conjugate of Tam in Figure 1 has 8 "haptens" (peptide antigens) and one "solid phase binding group" (-OH); this reads on the limitations of claim 100 with respect to numbers of entities.

With respect to the limitation that the amino acid carrier of the claimed conjugates is "non-immunologically reactive", Tam disclose that their dendritic core molecule (i.e. the carrier) clearly is not antigenic thus is "non-immunologically reactive" (see, for example, column 3, lines 31-48 of the reference). Note that the instant specification states on page 16 (1st paragraph) that a "non-immunologically reactive" amino acid sequence is one that "does not interfere with the test procedure in the intended application". The carrier of Tam clearly meets this limitation for their intended application (see Examples 13 & 14 of the reference).

Response to Arguments

46. Applicant's arguments filed July 23, 2002 (Paper No. 32) have been fully considered but are not found persuasive. The examiner's rationale is set forth below. *Please also see paragraph 35 above.*

47. Applicants argue that Tam does not teach or suggest a conjugate having hapten molecules and marker groups "coupled to reactive side groups at predetermined positions" (Response, page 13). As stated in the written description rejection above, the term "predetermined positions" is *not adequately described* in the instant specification. Moreover, as the sequence and structure of the conjugate of Tam is known (e.g. Figure 1 of the reference), this would read on groups "coupled to reactive side groups at predetermined positions".

48. Applicants also argue that the conjugates of Tam would result "in binding of the carrier to a solid phase at a variety of statistically determined (as opposed to predetermined and controlled) positions thereon" (Response, pages 13-14). In response to these arguments, it is noted that the features upon which applicant relies (i.e. controlled incorporation) are not recited in the rejected claim(s). Additionally, as the sequence and structure of the conjugate of Tam is ***known*** (e.g. Figure 1 of the reference), these arguments are moot for this reason as well.

49. For these reasons, the rejection of claims 72, 74, 75, 80, 86, 87, 88, 100 and 106 under 35 U.S.C. 102(b) as being anticipated by Tam is maintained.

50. Claims 72, 74, 75, 76, 80, 86, 87, 88, 100 and 106 are rejected under 35 U.S.C. 102(e) as being anticipated by Rose et al (US 6,001,364).

Rose et al disclose compositions of matter comprising "baseplates having a plurality of oxime forming complementary reactive groups" that are attached to "reactive molecules" (see Abstract). The multivalent molecules of Rose et al (see column 7, lines 16-22) read on the claimed conjugates as described below.

The "polymeric carrier" in Rose et al consists of their "baseplate" molecule (see column 7, lines 26-37) which in Figure 1 is shown as consisting of 9 amino acid residues; this reads on the limitations of claims 74 and 75 where the monomers are amino acids and the carrier has 9 monomeric units. Six peptide antigens (i.e. hapten) moieties are attached to the "baseplate" molecule of Rose et

al in Figure 1, reading on the limitations of claim 76. The haptens are attached to reactive amino groups (Lys and amine terminus) of the carrier (see column 3, lines 63-65 and column 10, lines 30-44), which reads on the limitations of claim 80.

Applicant's recited definition of hapten (see instant specification page 8) encompasses any molecule that is a "pharmacological active substance". The peptide active molecules of Rose et al (denoted COSMs) are known to be "pharmacologically active substances" (claim 87) and have molecular weights of greater than 100 (claim 86). The COSMs of Rose et al specifically read on the exact same "immunogenically reactive peptide epitope" haptens claimed in the instant claim 88. See discussion of peptide COSMs found in Rose et al column 5, line 60 through column 6, line 17. See also Example II which describes the synthesis and origin of the various peptide COSMs.

The conjugates of Rose et al are made on a solid support via coupling at one end of the molecule (at the –OH moiety of the 1st amino acid of the baseplate) and thus have a "solid phase binding group" of -OH; see solid phase synthesis of the baseplate described in Example I of the reference. Thus the conjugate of Rose et al in Figure 1 has a peptide "baseplate" of sequence GGGKKKKKG; 6 "haptens" (peptide COSMs of sequence KLEEQRPERVKG) and one "solid phase binding group" (-OH); this reads on the limitations of claim 100 with respect to numbers of entities. Moreover, Rose et al teach a conjugate containing a biotin group which would also read on the claimed "solid phase binding group",

see Example VIII in column 22 of the reference. Rose also teaches conjugates attached to a solid surface via thiol chemistry, see Example VIII in column 22-23.

With respect to the limitation that the amino acid carrier of the claimed conjugates is "non-immunologically reactive", Rose et al disclose that their "baseplate" (i.e. the carrier) clearly is not antigenic thus is "non-immunologically reactive" (see, for example, column 14, lines 7-26 of the reference). Note that the instant specification states on page 16 (1st paragraph) that a "non-immunologically reactive" amino acid sequence is one that "does not interfere with the test procedure in the intended application". The carrier of Rose et al clearly meets this limitation for their intended applications (see column 15, line 62 through column 16, line 22 and Example VII).

Response to Arguments

51. Applicant's arguments filed July 23, 2002 (Paper No. 32) have been fully considered but are not found persuasive. The examiner's rationale is set forth below. *Please also see paragraph 35 above.*

52. Applicants argue that Rose does not teach or suggest a conjugate having hapten molecules and marker groups "coupled to reactive side groups at predetermined positions" (Response, page 14). As stated in the written description rejection above, the term "predetermined positions" is *not adequately described* in the instant specification. Moreover, as the sequence and structure of the conjugate of Rose is known (e.g. Figure 1 of the

reference), this would read on groups "coupled to reactive side groups at predetermined positions".

53. Applicants also argue that the conjugates of Rose would result "in binding of the carrier to a solid phase at a variety of statistically determined (as opposed to predetermined and controlled) positions thereon" (Response, pages 15). In response to these arguments, it is noted that the features upon which applicant relies (i.e. controlled incorporation) are not recited in the rejected claim(s). Additionally, as the sequence and structure of the conjugate of Rose is ***known*** (e.g. Figure 1 of the reference), these arguments are moot for this reason as well.

54. For these reasons, the rejection of claims 72, 74, 75, 76, 80, 86, 87, 88, 100 and 106 under 35 U.S.C. 102(e) as being anticipated by Rose et al is maintained.

Maintained Rejections
Claim Rejections - 35 USC § 103

55. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

56. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

57. Claims 72, 74, 75, 80, 81, 86, 87, 88, 100, 103, 104 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tam (US 5,229,490).

The teachings of Tam are set forth supra. The reference lacks the specific exemplification of using "artificial" amino acids, specifically β-alanine, in the polymeric carrier (instant claims 103 & 104). The reference also lacks the specific exemplification of using a labeling group (i.e. the instant "marker groups" of claim 81).

However, the reference sets forth in column 5, lines 27-32 that the use of additional residues in extending the dendritic core molecule ("polymeric carrier") for peptide antigens of short chain length (6-14 residues) is preferred. The reference specifically sets forth β-alanine for such a purpose (column 5, line 30).

Also, Tam teaches that in using their conjugates for testing that "the diagnostic moiety joined to the dendritic polymer may be labeled with a

detectable label" (column 10, lines 44-55). The reference sets forth fluorescent labels as a "useful" type of such groups (column 10, lines 48-50).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use β-alanine as a part of the dendritic core molecule ("polymeric carrier") of Tam and/or use a detectable fluorescent label as the reference describes these modifications specifically. One of ordinary skill would have been motivated to use β-alanine in the carrier when the peptide antigen of interest is of short chain length (6-14 residues) as set forth by Tam. One of ordinary skill would have been motivated to use a detectable fluorescent label when necessary for the test of interest as set forth by Tam (see column 10, lines 40-55). One of ordinary skill would also have had a reasonable expectation of success based on the fact that the synthesis of the polymeric carriers of Tam are carried out using standard techniques thus were well known and routine in the art at the time of filing (see Example 1 of the reference). Methods of labeling are also well known, as taught by Tam (column 10, lines 54-55).

Response to Arguments

58. Applicant's arguments filed July 23, 2002 (Paper No. 32) have been fully considered but are not found persuasive. The examiner's rationale is set forth in paragraphs 62-63 below.

59. Claims 72, 73, 74, 75, 76, 80, 81, 86, 87, 88, 100, 103 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rose et al (US 6,001,364).

The teachings of Rose et al are set forth supra. The reference lacks the specific exemplification of using "artificial" amino acids in the polymeric carrier (instant claims 103). The reference also lacks the specific exemplification of using a labeling group, specifically metal chelates (i.e. the instant "marker groups" of claim 73 & 81).

However, the reference sets forth in column 7, line 23 through column 8, line 2 that the use of "artificial" amino acid residues in the baseplate molecule (i.e. "polymeric carrier") is preferred. The reference specifically sets forth using β-amino acids for such a purpose (column 7, line 37-41 & column 7, line 66 through column 8, line 2).

Also, Rose et al teaches that in their conjugates can comprise metal chelates as they are also considered to be haptens (see column 6, lines 13-17; column 12, line 62 through column 13, line 13 & column 14, lines 12-26) and/or can be a part of the complementarity determining region of an antibody (see column 14, lines 39-46). The reference also teach polyoxime conjugates containing "signal producing groups" (see Example VIII in column 22) and the use of "reporter groups" (column 13, lines 46-64) all reading in the instant "marker groups".

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use β-amino acids as a part of the basplate

("polymeric carrier") of Rose et al and/or use a detectable signal or reporter groups that are metal chelates as the reference describes these modifications specifically. One of ordinary skill would have been motivated to use β-amino acids in the carrier as these are preferred residues as set forth by Rose (column 7, line 66 through column 8, line 2). One of ordinary skill would have been motivated to use a detectable signal or reporter groups that are metal chelates when necessary for the test of interest as set forth by Rose (see column 13, lines 53-65 & column 14, lines 42-46). One of ordinary skill would also have had a reasonable expectation of success based on the fact that the synthesis of the polymeric carriers of Rose are carried out using standard techniques thus were well known and routine in the art at the time of filing (see Example 1 of the reference). Methods of labeling are also well known, as taught by Rose (column 14, lines 21-23 & 42-50).

Response to Arguments

60. Applicant's arguments filed July 23, 2002 (Paper No. 32) have been fully considered but are not found persuasive. The examiner's rationale is set forth in paragraphs 62-63 below.

61. Claims 72-77, 80, 81, 83, 84, 86, 87, 101, 103, 105 and 106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst et al (Anal. Biochem., 1991; of record) in view of Bard (US 5,310,687; of record).

The teachings of Bredehorst et al are set forth supra. The reference lacks the specific use of a luminescent metal chelate as the "marker group" (claims 73 and 84).

However, the use of luminescent metal chelates as marker or labeling groups in conjugates was well known in the art at the time of filing. For example, Bard et al teach electrochemiluminescent organometallic compounds that are used as labels for detecting low concentrations of chemical moieties (see Abstract). Bard et al describe using their luminescent metal chelates in a variety of systems (see column 1, lines 13-33) and specifically set forth that the metal chelates are covalently attached to a biological substance (see patented claim 1 and column 9, lines 7-40). Specific chelates are described by Bard in columns 10-11 of the reference. Bard et al teach that suitable conditions for creating the conjugates are known in the art (column 13, lines 34-43, for example) and also specifically teach attaching their luminescent metal chelates to BSA and antibodies (see Examples III, IV and V of the reference).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the luminescent metal chelates of Bard in place of the fluorophore of Bredehorst as both the metal chelate and the Bredehorst are known in the art to be marker or labeling groups. One of ordinary skill would have been motivated to do so as the metal chelates of Bard allow for detection at low concentrations (see Abstract) and provide measurements that are "sensitive, fast, reproducible and utilize simple instrumentation" (see column 12,

lines 50-68). Furthermore, Bard et al specifically teach that their luminescent metal chelates are superior to a fluorphore in a comparison study (See Example VII of the reference).

Response to Arguments

62. Applicant's arguments filed July 23, 2002 (Paper No. 32) have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

63. Applicant argues that because Tam, Rose and Bredehorst do not disclose the invention as argued for the rejections under 35 USC 102, the rejections under 35 USC 103 based on these references are also improper. The examiner respectfully disagrees. As the examiner's position is that each of the Tam, Rose and Bredehorst references *does* disclose the claimed invention (see Response to Arguments sections for each rejection), each of the rejections under 35 USC 103 is maintained.

Status of Claims/Conclusion

64. No claims are allowed.

65. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply

is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

66. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner is on an increased flextime schedule but can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

67. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached at (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie Garcia Baker, Ph.D.
May 18, 2003

MAURIE GARCIA BAKER PH.D
PRIMARY EXAMINER